UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO
10/014,485	11/13/2001	Michael J. Comb	CST-138 CIP2	4101

31012 7590 10/20/2004

JAMES GREGORY CULLEM, ESQ.
INTELLECTUAL PROPERTY COUNSEL
CELL SIGNALING TECHNOLOGY, INC.
166B CUMMINGS CENTER
BEVERLY, MA 01915

EXAMINER	
CANELLA, KAREN A	
ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 10/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/014,485	COMB ET AL.	
	Examiner	Art Unit	
	Karen A Canella	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4 and 11-45* is/are pending in the application.

4a) Of the above claim(s) *1,17-20,22 and 27-45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-4,11-16,21 and 23-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/13/01*. + 3/18/2004
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgement is made of applicant election with traverse of Group I and the species of Akt. The traversal is on the grounds that the restriction is improper because it separates overlapping subject matter. This has been considered and found persuasive. Group II is hereby rejoined to Group I. Further, after review of the prior art, the requirement for the species election is also withdrawn.

Claims 5-10 have been canceled. Claims 2-4, 11-13, 15, 16, 21 and 23-25 have been amended. Claims 1-4, 11-45 are pending. Claims 1, 17-20, 22 and 27-45, drawn to non-elected inventions, are withdrawn from consideration. Claims 2-4, 11-16, 21 and 23-26 are examined on the merits.

The specification is objected to for not reciting the updated statuses of the priority applications.

Claims 11, 12, 13, 24 and 25 are object to for recited non elected inventions.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 21 and 23 are rejected under 35 U.S.C. 102(b) as being anticipated by Mandelkow et al (EP 544,942) as evidenced by Paul (Fundamental Immunology (text), 1993, pp. 242-243).

Claim 21 is drawn to a motif-specific context impendent antibody that specifically binds a recurring, phosphorylated motif comprising two to six invariant amino acids, said antibody specifically binding said motif in a plurality of peptides or proteins within an organism in which it occurs. It is noted that section II of the claim is optional. Claim 23 embodies the antibody of claim 21 which consists of all or a part of a kinase consensus substrate motif or a potein-protien binding motif.

Mandelkow et al disclose the antibodies SM133 and SM134 which recognize phosphorylated human tau in normal individuals and PHF tau from individuals having Alzheimer disease (page 8, lines 54-57). It is noted in figures 12 c and d that the antibodies react with more than one isoform of tau protein as indicated by the gel. Thus, the antibody reacts with a plurality of peptides or proteins within the human. Mandelkow et al do not specifically disclose that the SM133 and SM134 antibodies react with a phosphorylated epitope of two to six invariant amino acids, however one of skill in the art would conclude that because an antigenic epitope is commonly six amino acids (Paul, page 243, first column, lines 7-10), the epitope recognized by SM133 and SM134 would comprise six amino acids.

Mandelkow et al disclose the specific embodiments of claim 23, because "part" of a kinase consensus substrate motif or a protein-protein binding motif can be a single amino acid, such as phosphorylated Serine, Proline or "X".

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 2, 3, 4, 11, 21 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mandelkow et al (EP 544,942) as evidenced by Paul (Fundamental Immunology (text), 1993, pp. 242-243) in view of Pinilla et al (Peptide Research, 1995, Vol. 8, pp. 250-257).

The specific embodiments of claims 21 and 23 are set forth above.

Claim 3 is drawn to a method for producing a motif-specific context independent antibody that specifically binds a recurring modified motif in a plurality of peptide or proteins within an organism in which it recurs, said method comprising the steps of constructing a degenerate peptide library comprising a fixed target motif comprising two to six invariant amino acids including at least one modified amino acid and optionally one or more degenerate amino acid positions and a plurality of degenerate amino acids flanking said motif; immunizing a host with said peptide library and isolating antisera from the host, purifying the motif-specific, context independent antibody, said antibody specifically binding said motif in a plurality of peptides or proteins within an organism in which it recurs. Claim 2 embodies the method of claim 3 further comprising the step of utilizing spleen cells from the host of step(b) to generate at least one monoclonal, motif-specific context impendent antibody. Claim 4 embodies the method of claim 3 wherein said modified amino acid is a phosphorylated, acetylated, methylated or nitrosylated. Claim 11 embodies the method of claim 3 wherein said target motif comprises all or part of a kinase consensus substrate motif or a potein-protien binding motif.

Mandelkow et al teach peptides comprising Ser-Pro or Thr-Pro motifs which are of potential diagnostic value for Alzheimer's Disease, wherein Ser or Thr are in the phosphorylated or non-phosphorylated state (page 16, lines 1-48). Examination of these peptides indicates that SEQ ID NO:9 and SEQ ID NO:11-21 comprise a Thr-Pro. SEQ ID NO:1-8 and 10 comprise a Ser-Pro. Thus, one of skill in the at can see that these peptides can be represented by the epitope (Ser/Thr) Pro. Mandelkow et al teach that the tau protein from Alzheimer's patients react with certain antibodies in a phosphorylation dependent manner and exhibit a lower electrophoritic mobility which may be related to a soecial phosphorylation status (page 2, lines 18-22). Mandelkow et al do not teach a method for making a motif-specific, context-indepednt antibody which would bind to all of the SEQ ID NO:1-21 when T or S were phosphorylated.

Pinilla et al teach a method of using a synthetic combinatioral peptide library for determining antibody polyspecificity. Pinilla et al teach that peptide antigenic determinants were

found to contain one to three highly specific residues, as well as one to two positions that can be considered as redundant (page 250, right column, lines 4-11). Pinilla et al teach that a number of studies using peptide libraries have found a variety of unrelated sequences recognized by monoclonal antibodies (page 250, right column, lines 49-52). Piniall et al conclude that the results of the aforesaid studies suggest that the concept of monoclonal antibody polyspecificity which is usually associated with natural and pre-immune antibodies having low-affinities may be a feature of antibodies in general even for those antibodies having high affinities (page 250, right column, line 59 to page 251, left column, line 4). Pinilla et al teach that the mAb used to screen the peptide library was raised against the 14-mer peptide LHNNEAGRTTVFSC (page251, left column, lines 33-37) and that peptides which specifically bound to the antibody are set forth in Table 5 and include the sequence GRTTVF (page 254, Table 5). Because the antibody which was raised to LHNNEAGRTTVFSC also binds other peptides in Table 5, one of skill in the art would reasonably conclude that the mAb bound to a motif of peptides represented in part by (Gly-Arg)/(Arg-Gly) followed by Thr/Trp/Tyr/Ile, etc.

It would have been prima facie obvious at the time the claimed invention was made to make a monoclonal antibody which context –independent and specific for the motif (Ser*/Thr*) Pro. One of skill in the art would have been motivated to do so by the teachings of Mandelkow et al on the diagnostic importance of peptides comprising SEQ ID NO:1-10, and the importance of phosphorylation on Serine or Threonine in said peptides; and the teachings of Pinilla et al on the polyspecificity of monoclonal antibodies as a general phenomenon, even in high affinity antibodies. One of skill in the would conclude that it would be possible to deliberately screen for a polyspecific antibody having affinity for a peptide motif as indicated in Table 5 of Pinilla et al. One of skill in the art would be motivated to transfer this process to the isolation of a monoclonal antibody having a polyspecificity to the epitopes of SEQI DNO:1-10 as taught by Mandelkow et al in order to obtain a monoclonal antibody which reacted generally with (Ser*/Thr*) Pro in order to identify tau proteins or tissues expressing tau proteins which were highly phosphorylated in order to diagnose Alzheimer's disease.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 2-4, 11-14 and 16 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 and 5 of U.S. Patent No. 6,441,140 in view of Pearson et al (Protein Phosphorylation, G Hardie, ED, 1995, reference CX of the IDS filed November 13, 2001).

Claim 1 of the '140 patent is drawn to a method for producing a motif-specific, context-independent antibody that recognizes a plurality of peptides or proteins within a genome that contain the motif, said method comprising the steps of: (a) constructing a combinatorial peptide library comprising (i) a fixed motif, comprises a kinase consensus substrate motif or a protein-protein binding motif and wherein said fixed motif comprises at least one phosphorylated amino acid selected from the group consisting of phosphothreonine, phosphoserine, and phosphotyrosine, and (ii) a plurality of degenerate amino acids surrounding said motif; (b) immunizing a host with said peptide library; and (c) isolating antisera from said host, and purifying said motif-specific, context-independent antibody from said antisera, said antibody recognizing a plurality of peptides or a proteins with a genome that contain said motif. Claim 2 embodies the method of claim 1, further comprising the step of utilizing spleen cells from the

host of step (b) to generate at least one monoclonal, motif-specific, context-independent antibody. Claim 3 embodies method of claim 1, wherein said kinase consensus substrate motif is selected from the group consisting MAPK consensus substrate motifs and CDK consensus substrate motifs, and wherein said protein binding motif is a 14-3-3 binding motif. Claim 5 is drawn to the method of claim 1, in part, wherein said peptide library is from 6 to 14 amino acids. The claims of the '140 patent specify that the fixed motif comprises at least one phosphorylated amino acid but do not specify two to six invariant amino acids within the motif.

Pearson et al teach protein kinase recognition motifs having 2, 3, 4 and 5 invariant amino acid residues (Table 1) It would have been prima facie obvious at the time the claimed invention was made to use the motifs taught by Person et al to carry out the method of the '140 patent. One of skill in the art would have been motivated to do so because the specific motifs taught by Pearson et al are protein kinase consensus motif having at least one phosphorylate amino acid.

Claims 21, 23-26 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 28-33 and 40-44 of copending Application No. 09/535,364. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '364 application anticipate the instant claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10 a.m. to 9 p.m. M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571)272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D.
10/18/2004

KAREN A. CANELLA PH.D
PRIMARY EXAMINER